For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

OCABILE

1. **Generic Name**

Obeticholic acid Tablets 5 mg and 10 mg

2. Qualitative and quantitative composition

OCABILE 5

Each film coated tablet contains:

Obeticholic Acid. ……..5 mg

Excipients…… q.s.

Colours: Ferric Oxide USPNF Yellow & Titanium Dioxide I.P.

The excipients used are microcrystalline cellulose, Sodium starch glycolate, Magnesium stearate, Hydroxy propyl methyl cellulose, Talcum powder, Polyethylene glycol, Titanium dioxide, Ferric oxide Yellow

OCABILE 10

Each film coated tablet contains:

Obeticholic Acid. ……..10 mg

Excipients…… q.s.

Colours: Ferric Oxide USPNF Red & Titanium Dioxide I.P.

The excipients used are microcrystalline cellulose, Sodium starch glycolate, Magnesium stearate, Hydroxy propyl methyl cellulose, Talcum powder, Polyethylene glycol, Titanium dioxide, Ferric oxide red.

3. Dosage form and strength

Dosage form: Tablet

Strength: 5 and 10 mg

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid (UDCA) in adult with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

4.2 Posology and method of administration

Important Dosage and Administration Instructions

Prior to the initiation of Obeticholic acid in patients with suspected cirrhosis, use the nomogram (see Table 1) to calculate the patient's score to determine their Child-Pugh classification (A, B, or C) and determine the appropriate starting dosage (see Table 2).

Table 1: Child-Pugh Nomogram

Parameter	**Points Scored for Observed Findings**		
	1 point	2 points	3 points
Encephalopathy grade	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	< 2	2 to 3	> 3
Serum albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
International Normalized Ratio (INR)	< 1.7	1.7 to 2.2	> 2.2
Child-Pugh Class is obtained by adding the points from all 5 parameters to derive a total score, Which can range from 5 to 15 points. Child-Pugh Class A: 5 to 6 points Child-Pugh Class B: 7 to 9 points Child-Pugh Class C: 10 to 15 points			

Routinely monitor patients during Obeticholic acid treatment for biochemical response, tolerability, progression of PBC disease, and re-evaluate Child-Pugh classification to determine if dosage adjustment is needed. • Reduce the dosing frequency from once daily to once weekly as appropriate for patients who progress to advanced disease (i.e., from Child-Pugh Class A to Child-Pugh Class B or C).

Recommended Dosage Regimen

The recommended starting dose and titration dosage regimen of Obeticholic acid for patients who have not achieved an adequate biochemical response to an appropriate dosage of UDCA for at least 1 year or are intolerant to UDCA is dependent upon disease stage, as shown in Table 2:

• Non-cirrhotic patients or compensated cirrhotic patients with no or mild hepatic impairment (Child-Pugh Class A) are dosed once daily.

• Cirrhotic patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) or patients who have previously experienced a decompensation event are dosed initially once weekly and not more than twice weekly.

Table 2: Dosage Regimen by Disease Stage.

Staging / Classification	**Non-Cirrhotic or Compensated Child-Pugh Class A**	**Child-Pugh Class B or C or Patients with a Prior Decompensation Event**
Starting Obeticholic acid Dosage for first 3 months	5 mg once daily	5 mg once weekly

Staging / Classification	Non-Cirrhotic or Compensated Child-Pugh Class A	Child-Pugh Class B or C or Patients with a Prior Decompensation Event
Obeticholic acid Dosage Titration after first 3 months, for patients who have not achieved an adequate reduction in ALP and/or total bilirubin and who are tolerating Obeticholic acid	10 mg once daily	5 mg twice weekly (at least 3 days apart) Titrate to 10 mg twice weekly (at least 3 days apart) based on response and tolerability
Maximum Obeticholic acid Dosage	10 mg once daily	10 mg twice weekly (at least 3 days apart)
A Gastroesophageal variceal bleeding, new or worsening jaundice, spontaneous bacterial peritonitis, etc. b Prior to dosage adjustment, re-calculate the Child-Pugh classification		

Monitoring to Assess Safety, Treatment Interruption or Discontinuation.

Routinely monitor patients during Obeticholic acid treatment for progression of PBC disease with laboratory and clinical assessments to determine whether dosage adjustment is needed. Reduce the dosing frequency for patients who progress from Child-Pugh Class A to Child-Pugh Class B or C (see Table 2 above). Close monitoring is recommended for patients at an increased risk of hepatic

Decompensation, including those with laboratory evidence of worsening liver function (i.e., total bilirubin, INR, albumin) and/or progression to cirrhosis.

Interrupt treatment with Obeticholic acid in patients with laboratory or clinical evidence of worsening liver function indicating risk of decompensation, and monitor the patient's liver function.

If the patient's condition returns to baseline, weigh the potential risks and benefits of restarting Obeticholic acid tablet treatment. If Obeticholic acid tablet is re-initiated, use the recommended starting dosage with adjustment for Child-Pugh classification.

Consider discontinuing Obeticholic acid in patients who have experienced clinically significant liver-related adverse reactions.

Management of Patients with Intolerable Pruritus on Obeticholic acid

For patients with intolerable pruritus on Obeticholic acid, consider one or more of the following management strategies: For Non-Cirrhotic or Compensated Cirrhotic Child-Pugh Class A Patients:

• Add an antihistamine or bile acid binding resin

• Reduce the dosage of Obeticholic acid to: o 5 mg every other day, for patients intolerant to 5 mg once daily. o 5 mg once daily, for patients intolerant to 10 mg once daily.

• Temporarily interrupt Obeticholic acid dosing for up to 2 weeks. Restart at a reduced dosage. For patients whose dosage is reduced or interrupted, titrate the dosage based on biochemical response, tolerability and adjust according to Child-Pugh classification. For Child-Pugh Class B or C or Patients with a Prior Decompensation Event:

• Add an antihistamine or bile acid binding resin

• Temporarily interrupt Obeticholic acid dosing for up to 2 weeks. Restart at a reduced dosage if applicable. Titrate the dosage based on biochemical response, tolerability and adjust according to Child-Pugh classification.

Treatment Discontinuation

Consider discontinuing Obeticholic acid treatment in patients who continue to experience persistent, intolerable pruritus despite management strategies.

Administration Instructions

• Take Obeticholic acid with or without food.

• For patients taking a bile acid binding resin, take Obeticholic acid at least 4 hours before or 4 hours after taking the bile acid binding resin, or at as great an interval as possible.

4.3 Contraindications

Obeticholic acid tablet is contraindicated in patients with complete biliary obstruction.

4.4 Special warnings and precautions for use

Hepatic Decompensation and Failure in Incorrectly Dosed PBC Patients with Child-Pugh Class B or C or Decompensated Cirrhosis

In post marketing reports, hepatic decompensation and failure, in some cases fatal, have been reported in PBC patients with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment when Obeticholic acid was dosed more frequently than the recommended starting dosage of 5 mg once weekly. Reported cases typically occurred within 2 to 5 weeks after starting Obeticholic acid and were characterized by an acute increase in total bilirubin and/or ALP concentrations in association with clinical signs and symptoms of hepatic decompensation (e.g., ascites, jaundice, gastrointestinal bleeding, worsening of hepatic encephalopathy). A few cases reported improvement after Obeticholic acid discontinuation; however, some cases reported ongoing symptoms. Because post marketing cases often contain limited clinical information, there was insufficient information to rule out confounding factors (e.g., concomitant medications) or the role of the patient's underlying advanced disease in the events. Patients who died due to liver-related complications generally had decompensated cirrhosis prior to treatment and were started on Obeticholic acid 5 mg once daily, which is 7-fold greater than the once weekly starting regimen in this population.

Patient Management Routinely monitor patients for progression of PBC disease, including liver-related complications, with laboratory and clinical assessments. Dosage adjustment, interruption or discontinuation may be required. Close monitoring is recommended for patients at an increased risk of hepatic decompensation. Severe intercurrent illnesses that may worsen renal function or cause dehydration (e.g., gastroenteritis), may exacerbate the risk of hepatic decompensation. Interrupt treatment with Obeticholic acid in patients with laboratory or clinical evidence of worsening liver function indicating risk of decompensation, and monitor the patient's liver function. Consider discontinuing Obeticholic acid in patients who have experienced clinically significant liver-related adverse reactions. Discontinue Obeticholic acid in patients who develop complete biliary obstruction.

Liver-Related Adverse Reactions

In two 3-month, placebo-controlled clinical trials in patients with primarily early stage PBC disease, a dose-response relationship was observed for the occurrence of liver-related adverse reactions including jaundice, worsening ascites and primary biliary cholangitis flare with dosages of Obeticholic acid of 10 mg once daily to 50 mg once daily (up to 5-times the highest recommended dosage), as early as one month after starting treatment with Obeticholic acid. In a pooled analysis of three placebo-controlled trials in patients with primarily early stage PBC disease, the exposure-adjusted incidence rates for all serious and otherwise clinically significant liver-related adverse reactions, and isolated elevations in liver biochemical tests, per 100 patient exposure years (PEY) were: 5.2 in the Obeticholic acid 10 mg group (highest recommended dosage), 19.8 in the Obeticholic acid 25 mg group (2.5 times the highest recommended dosage) and 54.5 in the Obeticholic acid 50 mg group (5 times the highest recommended dosage) compared to 2.4 in the placebo group. Monitor patients during treatment with Obeticholic acid for elevations in liver biochemical tests and for the development of liver-related adverse reactions. Close monitoring is recommended for patients at an increased risk of hepatic decompensation. Interrupt treatment with Obeticholic acid in patients with laboratory or clinical evidence of worsening liver function indicating risk of decompensation, and monitor the patient's liver function.

Severe Pruritus

Severe pruritus was reported in 23% of patients in the Obeticholic acid 10 mg arm, 19% of patients in the Obeticholic acid titration arm, and 7% of patients in the placebo arm in Trial 1, a 12-month double-blind randomized controlled trial of 216 patients. Severe pruritus was defined as intense or widespread itching, interfering with activities of daily living, or causing severe sleep disturbance, or intolerable discomfort, and typically requiring medical interventions. In the subgroup of patients in the Obeticholic acid tablet titration arm who increased their dosage from 5 mg once daily to 10 mg once daily after 6 months of treatment (n=33), the incidence of severe pruritus was

0% from Months 0 to 6 and 15% from Months 6 to 12. The median time to onset of severe pruritus was 11, 158, and 75 days for patients in the Obeticholic acid 10 mg, Obeticholic acid titration, and placebo arms, respectively. Consider clinical evaluation of patients with new onset or worsening severe pruritus. Management strategies include the addition of bile acid resins or antihistamines, Obeticholic acid tablet dosage reduction, and/or temporary interruption of Obeticholic acid dosing.

Reduction in HDL-C

Patients with PBC generally exhibit hyperlipidemia characterized by a significant elevation in total cholesterol primarily due to increased levels of high density lipoprotein-cholesterol (HDL-C). In Trial 1, dose-dependent reductions from baseline in mean HDL-C levels were observed at 2 weeks in Obeticholic acid -treated patients, 20% and 9% in the 10 mg and titration arms, respectively, compared to 2% in the placebo arm. At month 12, the reduction from baseline in mean HDL-C level was 19% in the Obeticholic acid tablet 10 mg arm, 12% in the Obeticholic acid titration arm, and 2% in the placebo arm. Nine patients in the Obeticholic acid 10 mg arm, 6 patients in the Obeticholic acid titration arm, versus 3 patients in the placebo arm had reductions in HDL-C to less than 40 mg/dL. Monitor patients for changes in serum lipid levels during treatment. For patients

who do not respond to Obeticholic acid after 1 year at the highest recommended dosage that can be tolerated (maximum of 10 mg once daily), and who experience a reduction in HDL-C, weigh the potential risks against the benefits of continuing treatment

4.5 Drugs interactions

Bile Acid Binding Resins

Bile acid binding resins such as cholestyramine, colestipol, or colesevelam adsorb and reduce bile acid absorption and may reduce the absorption, systemic exposure, and efficacy of Obeticholic acid tablet. If taking a bile acid binding resin, take Obeticholic acid tablet at least 4 hours before or 4 hours after taking the bile acid binding resin, or at as great an interval as possible. Fertility, pregnancy and lactation.

Warfarin

The International Normalized Ratio (INR) decreased following coadministration of warfarin and Obeticholic acid. Monitor INR and adjust the dosage of warfarin, as needed, to maintain the target INR range when co-administering Obeticholic acid and warfarin.

CYP1A2 Substrates with Narrow Therapeutic Index

Obeticholic acid may increase the exposure to concomitant drugs that are CYP1A2 substrates. Therapeutic monitoring of CYP1A2 substrates with a narrow therapeutic index (e.g. theophylline and tizanidine) is recommended when co-administered with Obeticholic acid.

Inhibitors of Bile Salt Efflux Pump

Avoid concomitant use of inhibitors of the bile salt efflux pump (BSEP) such as cyclosporine. Concomitant medications that inhibit canalicular membrane bile acid transporters such as the BSEP may exacerbate accumulation of conjugated bile salts including taurine conjugate of obeticholic acid in the liver and result in clinical symptoms. If concomitant use is deemed necessary, monitor serum transaminases and bilirubin.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Risk Summary

The limited available human data on the use of obeticholic acid during pregnancy are not sufficient to inform a drug-associated risk. In animal reproduction studies, no developmental abnormalities or fetal harm was observed when pregnant rats or rabbits were administered obeticholic acid during the period of organogenesis at exposures approximately 13 times and 6 times human exposures, respectively, at the maximum recommended human dose (MRHD) of 10 mg [see Data below]. The Estimated background risks of major birth defects and miscarriage for the indicated population are

Unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively

Data

Animal Data

In an reported embryo-fetal development study in rats, obeticholic acid was administered orally during the period of organogenesis at doses of 5, 25, and 75 mg/kg/day. At 25 mg/kg/day (a dose that produced systemic exposures approximately 13 times those in humans at the MRHD of 10 mg), there was no maternal or developmental toxicity. At 75 mg/kg/day (approximately 40 times the human exposure at the MRHD), decreased fetal

body weights and increased numbers of early or late resorptions and nonviable fetuses were observed. In maternal animals, mortality, fetal loss, decreased body weight and food consumption as well as decreased body weight gain were observed at 75 mg/kg/day. Thus, the developmental toxicity observed at this dose may be secondary to maternal toxicity. In rabbits, obeticholic acid was administered orally during the period of organogenesis at doses of 3, 9, and 20 mg/kg/day. Obeticholic acid administered at doses up to 20 mg/kg/day (approximately 6 times the human exposure at the MRHD) was not teratogenic and did not produce any evidence of fetal harm.

In a pre- and post-natal development study, administration of obeticholic acid in rats during organogenesis through lactation at doses of 5, 25, and 40 mg/kg/day did not produce effects on pregnancy, parturition or postnatal development at any dose (the 40 mg/kg/day dose is approximately

21 times the human exposure at the MRHD). Obeticholic acid exposure margins were calculated using systemic exposure (AUC) values of obeticholic acid plus obeticholic acid's active metabolite conjugates (tauro-obeticholic acid and glycol-obeticholic acid) in animals (at the indicated doses) and in humans at the MRHD of 10 mg.

Lactation

Risk Summary

There is no information on the presence of obeticholic acid in human milk, the effects on the breast-fed infant or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Obeticholic acid and any potential adverse effects on the breastfed infant from Obeticholic acid or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of Obeticholic acid in pediatric patients have not been established.

Geriatric Use

Of the 201 patients in clinical trials of Obeticholic acid who received the recommended dosage (5 mg or 10 mg once daily), 41 (20%) were 65 years of age and older, while 9 (4%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and subjects less than 65 years of age, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment

Hepatic decompensation and failure, in some cases fatal, have been reported post marketing in PBC patients with decompensated cirrhosis or Child-Pugh B or C hepatic impairment when Obeticholic acid was dosed more frequently than recommended. In PBC clinical trials, a dose-response relationship was observed for the occurrence of liver-related adverse reactions with Obeticholic acid. Plasma exposure to obeticholic acid and its active conjugates, increases significantly in patients with moderate to severe hepatic impairment (Child-Pugh Classes B and C). Prior to the initiation of Obeticholic acid determine the patient's Child-Pugh classification to determine the starting dosage. Re-evaluate the dosing regimen periodically during treatment. Dosage adjustment is required in patients with Child-Pugh Class B and C. Routinely monitor patients for progression of PBC disease with laboratory and clinical assessments. Dosage adjustment, interruption or discontinuation may be required.

4.7 Effects on ability to drive and use machines.

Obeticholic acid has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The following clinically significant adverse reactions are described elsewhere in labeling:
• Hepatic Decompensation and Failure in Incorrectly Dosed PBC Patients with Child-Pugh Class B or C or Decompensated Cirrhosis.

• Liver-Related Adverse Reactions.

• Severe Pruritus [see Warnings and Precautions]

• Reduction in HDL-C [see Warnings and Precautions]

Clinical Trials Experience

Adverse reaction rates observed in the reported clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 432 patients with PBC were studied in three double-blind placebo-controlled trials. Of these patients, 290 were treated with Obeticholic acid for at least 6 months, 232 were treated for at least 12 months, and 70 were treated for at least 2 years. There were 131 patients who received Obeticholic acid 10 mg once daily and 70 who received Obeticholic acid 5 mg once daily.

In reported Trial 1, 216 patients were randomized (1:1:1) to receive either:,Obeticholic acid 10 mg once daily for the entire 12 months of the trial (n=73); Obeticholic acid titration (5 mg once daily for the initial 6 months, with the option to increase to 10 mg once daily for the last 6 months, in patients who were tolerating Obeticholic acid, but had ALP 1.67-times ULN or greater, and/or total bilirubin greater than ULN, or less than 15% ALP reduction) (n=70); or • placebo (n=73).

During the trial, Obeticholic acid or placebo was administered in combination with UDCA in 93% of patients and as monotherapy in 7% of patients who were unable to tolerate UDCA. The overall discontinuation rate was 12% in the Obeticholic acid 10 mg arm, 10% in the Obeticholic acid titration arm, and 4% in the placebo arm.

The recommended starting dosage of Obeticholic acid is 5 mg orally once daily for 3 months with titration to 10 mg once daily based upon tolerability and response. Initiation of therapy with Obeticholic acid 10 mg once daily is not recommended due to an increased risk of pruritus.

The most common adverse reactions in Trial 1 occurring in at least 5% of patients in either Obeticholic acid treatment arm and at an incidence at least 1% higher than the placebo treatment arm are shown in Table 3.

Table 3: Most Common Adverse Reactions in Adult Patients with PBC in Trial 1 by Treatment Arm with or without UDCAa.

Adverse Reaction[b]	Obeticholic acid tablet 10 mg N = 73 %	Obeticholic acid tablet Titration[c] N = 70 %	Placebo N = 73 %

Pruritus[d]	70	56	38
Fatigue[e]	25	19	15
Abdominal pain and discomfort	10	19	14
Rash[g]	10	7	8
Arthralgia	10	6	4
Oropharyngeal	8	7	1
Dizziness[h]	7	7	5
Constipation	7	7	5
Peripheral Edema	7	3	3
Palpitations	7	3	1
Pyrexia	7	0	1
Thyroid function	4	6	3
Eczema	3	6	0

In the reported trial there were 16 patients (7%) who were intolerant and did not receive concomitant UDCA:

6 patients (8%) in the Obeticholic acid 10 mg arm, 5 patients (7%) in the Obeticholic acid titration arm, and 5 patients (7%) in the placebo arm.

b Occurring in greater than or equal to 5% of patients in either Obeticholic acid t treatment arm and at an incidence greater than or equal to1% higher than in the placebo treatment arm.

c Patients randomized to Obeticholic acid titration received Obeticholic acid 5 mg once daily for the initial 6 month period. At Month 6, patients who were tolerating Obeticholic acid, but had an ALP 1.67-times ULN or greater, and/or total bilirubin greater than ULN, or less than 15% ALP reduction were eligible for titration from 5 mg once daily to 10 mg once daily for the final 6 months of the trial.

d Includes skin eruptions, prurigo, pruritus, pruritus generalized, eye pruritus, ear pruritus, anal pruritus, vulvovaginal pruritus, and rash pruritic.

e Includes fatigue, tiredness and asthenia.

f Includes abdominal pain upper, abdominal pain, abdominal discomfort, abdominal pain lower, abdominal tenderness, and gastrointestinal pain.

g Includes urticaria, rash, rash macular, rash papular, rash maculo-papular, heat rash, urticaria cholinergic.

h Includes dizziness, syncope, presyncope

i Includes thyroxine free decreased, blood thyroid stimulating hormone increased, hypothyroidism.

Liver-Related Adverse Reactions

In Trial 1, the following serious or otherwise clinically significant liver-related adverse reactions were reported at the recommended dosage of Obeticholic acid one patient in the Obeticholic acid 10 mg treatment arm experienced ascites; one patient in the Obeticholic acid titration treatment arm experienced two episodes of ascites and four episodes of hepatic encephalopathy; one patient in the placebo treatment arm experienced variceal bleeding.

Pruritus

Approximately 60% of patients had a history of pruritus upon enrollment in Trial 1. Treatment-emergent pruritus, including all the terms described in Table 3, generally started within the first month following the initiation of treatment with Obeticholic acid tablet.

The incidence of pruritus was higher in patients who started on Obeticholic acid 10 mg once daily relative to the Obeticholic acid tablet titration arm, 70% and 56%, respectively. Discontinuation rates due to pruritus were also higher in patients who started on Obeticholic acid 10 mg once daily relative to the Obeticholic acid titration arm, 10% and 1%, respectively.

The number of patients with pruritus who required an intervention (e.g., dosage adjustment, treatment interruption, or initiation of bile acid binding resin or antihistamine) was 30 of 51 patients (59%) in the Obeticholic acid 10 mg arm, 24 of 39 patients (62%) in the Obeticholic acid titration arm, and 14 of 28 patients (50%) in the placebo arm.

Post marketing Experience

The following adverse reactions have been identified during post approval use of Obeticholic acid. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure, particularly in PBC patients who have progressive liver disease.

Hepatobiliary Disorders: liver failure, new onset cirrhosis, increased direct and total bilirubin, new or worsening of jaundice, ascites, worsening hepatic encephalopathy

4.9 Overdose

In PBC patients who received Obeticholic acid 25 mg once daily (2.5 times the highest recommended dosage) or 50 mg once daily (5 times the highest recommended dosage), a dose-dependent increase in the incidence of liver-related adverse reactions, including elevations in liver biochemical tests, ascites, jaundice, portal hypertension, and primary biliary cholangitis flare, was reported. Serious liver-related adverse reactions have been reported postmarketing in PBC patients with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment when Obeticholic acid was dosed more frequently than the recommended starting dosage of 5 mg once weekly. In the case of overdosage, patients should be carefully observed and supportive care administered, as appropriate.

5. Pharmacological properties.

5.1 Mechanism of Action

Obeticholic acid is an agonist for FXR, a nuclear receptor expressed in the liver and intestine. FXR is a key regulator of bile acid, inflammatory, fibrotic, and metabolic

pathways. FXR activation decreases the intracellular hepatocyte concentrations of bile acids by suppressing de novo synthesis from cholesterol as well as by increased transport of bile acids out of the hepatocytes. These mechanisms limit the overall size of the circulating bile acid pool while promoting choleresis, thus reducing hepatic exposure to bile acids.

5.2 Pharmacodynamic properties

Pharmacodynamic Markers

In Trial 1, administration of Obeticholic acid 10 mg once daily was associated with a 173% increase in concentrations of FGF-19, an FXR-inducible enterokine involved in bile acid homeostasis, from baseline to Month 12. Concentrations of cholic acid and chenodeoxycholic acid were reduced 2.7 micromolar and 1.4 micromolar, respectively, from baseline to Month 12. The clinical relevance of these findings is unknown.

Cardiac Electrophysiology

At a dose of 10-times the maximum recommended dose, Obeticholic acid does not prolong the QT interval to any clinically relevant extent.

5.3 Pharmacokinetic properties

Absorption

Following multiple oral doses of Obeticholic acid 10 mg once daily, peak plasma concentrations (Cmax) of obeticholic acid occurred at a median time (Tmax) of approximately 1.5 hours. The median Tmax for both the glyco- and tauro-conjugates of obeticholic acid was 10 hours. Coadministration with food did not alter the extent of absorption of obeticholic acid. Following multiple-dose administration of Obeticholic acid tablet 5, 10, and 25 mg once daily (2.5 times the highest recommend dosage) for 14 days, systemic exposures of obeticholic acid increased dose proportionally. Exposures to glyco-obeticholic acid and tauro-obeticholic acid, and total obeticholic acid (the sum of obeticholic acid and its two active conjugates) increased more than proportionally with dose. The steady-state systemic exposure (AUC0-24h) achieved on Day14 of total obeticholic acid was 4.2-, 6.6-and 7.8- fold the systemic exposure (AUC0-24h) achieved on Day 1 after 5, 10, and 25 mg once daily dosing, respectively.

Distribution

Human plasma protein binding of obeticholic acid and its conjugates is greater than 99%. The volume of distribution of obeticholic acid is 618 L. The volumes of distribution of glyco- and tauro-obeticholic acid have not been determined.

Elimination

Metabolism: Obeticholic acid is conjugated with glycine or taurine in the liver and secreted into bile. These glycine and taurine conjugates of obeticholic acid are absorbed in the small intestine leading to enterohepatic recirculation. The conjugates can be deconjugated in the ileum and colon by intestinal microbiota, leading to the conversion to obeticholic acid that can be reabsorbed or excreted in feces, the principal route of elimination.

After daily administration of obeticholic acid, there was accumulation of the glycine and taurine conjugates of obeticholic acid, which have in vitro pharmacological activities similar to the parent drug, obeticholic acid. The metabolite-to-parent ratios of the glycine and taurine conjugates of obeticholic acid were 13.8 and 12.3 respectively, after daily

administration. An additional third obeticholic acid metabolite, 3-glucuronide, was formed but was considered to have minimal pharmacologic activity.

Excretion: After administration of radiolabelled obeticholic acid, about 87% of the dose was excreted in feces through biliary secretion. Less than 3% of the dose was excreted in the urine with no detection of obeticholic acid.

Specific Populations

Body weight, Age, Sex Race/Ethnicity: Based on population pharmacokinetic analysis, body weight was a significant predictor of obeticholic acid pharmacokinetics with lower obeticholic acid exposure expected with higher body weight. The body weight effect is not expected to cause a meaningful impact on efficacy. The pharmacokinetics of obeticholic acid would not be expected to be altered based on age, sex, or race/ethnicity.

Renal Impairment: Obeticholic acid has not been studied in patients with moderate and severe renal impairment (estimated glomerular filtration rate [eGFR] less than 60 mL/min/1.73 m2). In the population pharmacokinetic analysis, an eGFR greater than 50 mL/min/1.73 m2 did not have a meaningful effect on the pharmacokinetics of obeticholic acid and its conjugated metabolites.

Hepatic Impairment: Obeticholic acid is metabolized in the liver. In subjects with mild, moderate and severe hepatic impairment (Child-Pugh Class A, B, and C, respectively), the mean AUC of total obeticholic acid increased 1.1-, 4- and 17-fold, respectively, compared to subjects with normal hepatic function following single-dose administration of 10 mg Obeticholic acid tablet.

Drug Interaction Studies

Effect of Obeticholic Acid on Other Drugs

Based on in vitro studies, obeticholic acid can inhibit CYP3A4. However, an in vivo study indicated no inhibition of CYP3A4 by obeticholic acid at the recommended dose of Obeticholic acid tablet. Obeticholic acid is not expected to inhibit CYPs 2B6, 2C8, 2C9, 2C19, and 2D6, or induce CYPs

1A2, 2B6, 2C8, 2C9, 2C19, and 3A4 at the recommended dose of Obeticholic acid tablet. Down-regulation of mRNA was observed in a concentration-dependent fashion for CYP1A2 and CYP3A4 by obeticholic acid and its glycine and taurine conjugates

In vitro studies suggest that there is potential for obeticholic acid and its glycine and taurine conjugates to inhibit OATP1B1 and OATP1B3 (the clinical significance of which is unknown), but not P-gp, BCRP, OAT1, OAT3, OCT2, and MATE transporters, at the recommended dose of Obeticholic acid.

In vitro studies showed that obeticholic acid and its glycine and taurine conjugates inhibit BSEP in a dose dependent manner. However, an in vivo drug interaction due to inhibition of BSEP in patients using the recommended dosage regimen appears unlikely

Induction of BSEP can occur by FXR activation by obeticholic acid and its conjugates, which are FXR agonists

Warfarin: Concomitant administration of 25 mg warfarin as a single dose with Obeticholic acid 10 mg once daily resulted in 13% increase in systemic exposure to S-warfarin and 11% decrease in maximum INR.

Caffeine (CYP1A2 substrate): Concomitant administration of 200 mg caffeine as a single dose with Obeticholic acid 10 mg once daily resulted in a 42% increase in plasma AUC and 6% increase in Cmax of caffeine.

Omeprazole (CYP2C19 substrate): Concomitant administration of 20 mg omeprazole as a single dose with Obeticholic acid 10 mg once daily resulted in a 32% increase in AUC and a 33% increase in Cmax of omeprazole. The clinical significance is unknown.

No clinically relevant interactions were seen when the following drugs were administered as single doses concomitantly with Obeticholic acid 10 mg once daily:

Midazolam 2 mg (CYP3A4 substrate): 2% increase in AUC and Cmax of midazolam Dextromethorphan 30 mg (CYP2D6 substrate): 11% decrease in AUC and 12% decrease in Cmax of dextromethorphan..

Digoxin 0.25 mg (P-gp substrate): 1% increase in AUC and 3% decrease in Cmax of digoxin.

Rosuvastatin 20 mg (BCRP, OATP1B1, OATP1B3 substrate): 22% increase in AUC and a 27% increase in Cmax of rosuvastatin.

Effect of Other Drugs on Obeticholic Acid

In vitro data suggest that obeticholic acid is not metabolized to any significant extent by CYP450 enzymes.

Proton Pump Inhibitors (omeprazole): Concomitant administration of 20 mg omeprazole once daily with Obeticholic acid 10 mg once daily resulted in a less than 1.2-fold increase in obeticholic acid exposure.

This increase is not expected to be clinically relevant. Concomitant administration of 40 mg omeprazole once daily with Obeticholic acid 10 mg once daily was not studied.

BSEP inhibitors: In vitro data indicate that tauro-obeticholic acid is a substrate of BSEP

6. Nonclinical properties\

6.1 Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

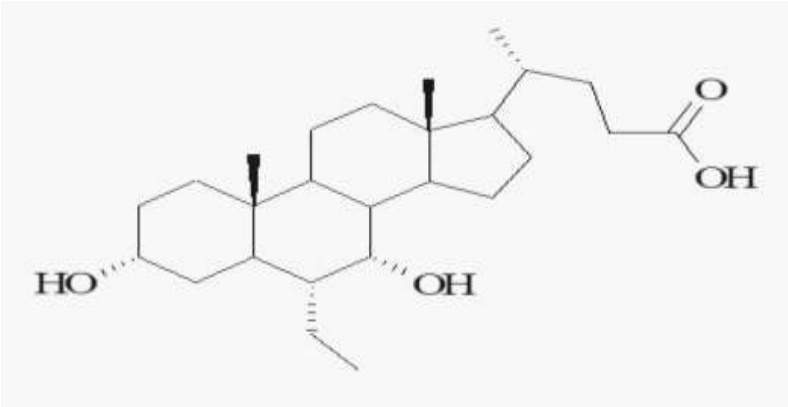
Carcinogenic potential of obeticholic acid was assessed in carcinogenicity studies of up to 2 years in duration in mice and rats. In mice, there were no drug-related neoplastic findings at doses up to 25 mg/kg/day obeticholic acid, a dose that produced systemic exposures approximately 12 times those in humans at the MRHD of 10 mg. In rats, obeticholic acid was administered at doses of 2, 7, and 20 mg/kg/day. At 20 mg/kg/day (approximately 12 times the human exposure at the MRHD), obeticholic acid caused an increase in the incidence of benign granulosa cell tumors in the ovaries and benign granular cell tumors in the cervix and vagina of female rats. There were no drug-related neoplastic findings in male rats.

Obeticholic acid was not genotoxic in the Ames test, a human peripheral blood lymphocyte chromosomal aberration test, and a mouse micronucleus test. The glycine conjugate of obeticholic acid was also not genotoxic in an Ames test and human peripheral blood lymphocyte chromosome aberration test. The taurine conjugate of obeticholic acid was not genotoxic in an Ames test, and was negative in a human peripheral blood lymphocyte chromosomal aberration test in the presence of metabolic activation; the findings of the chromosomal aberration assay in the absence of metabolic activation were inconclusive.

Obeticholic acid, administered at oral doses of 5, 25 and 50 mg/kg/day to male rats for 28 days before mating and throughout the mating period, and to female rats from 14 days before mating through mating and until gestation day 7, did not alter male or female fertility or early embryonic development at any dose (the 50 mg/kg/day dose is approximately 13 times the human exposure at the MRHD).

7. Description

Obeticholic acid is a farnesoid X receptor (FXR) agonist. Chemically, obeticholic acid is 3a, 7a-dihydroxy- 6a-ethyl-5ß-cholan-24-oic acid. It is a white to off-white powder. It is soluble in methanol, acetone and ethyl acetate. Its solubility in water is pH dependent. It is slightly soluble at low pH and very soluble at high pH. Its chemical formula is $C_{26}H_{44}O_4$, the molecular weight is420.63 g/mol and the chemical structure is:



OCABILE 5 is Yellow coloured, round, biconvex, both side plain and film coated tablets. The excipients used are microcrystalline cellulose, Sodium starch glycolate, Magnesium stearate, hydroxy propyl methyl cellulose, Talcum powder, Polyethylene glycol, Titanium dioxide, Ferric oxide yellow

OCABILE 10 is Reddish brown coloured, round, biconvex, both side plain and film coated tablets. The excipients used are microcrystalline cellulose, Sodium starch glycolate, Magnesium stearate, hydroxy propyl methyl cellulose, Talcum powder, Polyethylene glycol, Titanium dioxide, Ferric oxide red

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

OCABILE 5 and OCABILE 10 are packed in Alu- Alu blister of 10 tablets.

8.4 Storage and handing instructions

STORE PROTECTED FROM LIGHT & MOISTURE, AT A TEMPERATURE. NOT EXCEEDING 30°C

9. Patient counselling information

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What OCABILE is and what it is used for

OCABILE contains the active substance obeticholic acid (farnesoid X-receptor agonist) which helps to improve how your liver works by reducing the production and build-up of bile in the liver and also reducing inflammation. This medicine is used for the treatment of for the treatment of primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid (UDCA) in adult with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

9.2 What you need to know before you take OCABILE

Do not take OCABILE**:**

- If you are allergic to OCABILE or any of the other ingredients of this medicine.

- If you have a complete blockage of the biliary tract (liver, gall bladder and bile ducts).

Warnings and precautions

Talk to your doctor or pharmacist before taking OCABILE.

If you experience itching that is difficult to tolerate, talk to your doctor.

Your doctor will do blood tests to monitor the health of your liver when you start treatment and regularly from there on.

Children and adolescents

This medicine is not for use in children or adolescents.

Other medicines and OCABILE

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. In particular, tell your doctor if you are taking so-called bile acid binding resins (cholestyramine, colestipol, and colesevelam) used to lower blood cholesterol levels as they may lessen the effect of OCABILE. If you take any of these medicines, take

OCABILE at least 4-6 hours before or 4-6 hours after taking bile acid binding resin, giving as much time as possible.

The levels of some medicines such as theophylline (a medicine to help breathing) or tizanidine (a medicine to relieve the stiffness and restriction of muscles) may be increased and need to be monitored by your doctor while taking OCABILE. Your doctor may need to monitor how well your blood clots when taking medicines such as warfarin (a medicine to help your blood flow) with OCABILE.

Pregnancy and breast-feeding

There is little information about the effects of OCABILE in pregnancy. As a precautionary measure, you should not take OCABILE if you are pregnant.

It is not known if this medicine passes into human milk. Your doctor will determine whether you should discontinue breast-feeding or discontinue/abstain from OCABILE therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for you.

Driving and using machines

This medicine has no or negligible influence on your ability to drive or use machines

9.3 How to take OCABILE

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one 5 mg film-coated tablet once daily by mouth.

Your doctor may adjust your dose depending on your liver function or if you experience itching that is difficult to tolerate.

Depending on your body's response after 6 months your doctor may increase your dose to 10 mg once daily. Your doctor will discuss any change of dose with you.

You can take OCABILE with or without food. If you take bile acid binding resins, take this medicine at least 4-6 hours before or at least 4-6 hours after the bile acid binding resin (see section "Other medicines and OCABILE ").

If you take more OCABILE than you should

If you accidentally take too many tablets, you may experience liver related side effects such as yellowing of the skin. Contact a doctor or go to a hospital for advice immediately.

If you forget to take OCABILE

Skip the missed dose and take your next dose when you would normally take it. Do not take a double dose to make up for a forgotten tablet.

If you stop taking OCABILE

You should continue to take OCABILE for as long as your doctor tells you to. Do not stop taking the medicine without talking to your doctor first. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor or pharmacist if you experience itching of the skin (pruritus) or if the itch gets worse while on this medicine. In general itching of the skin is a very common

side effect that begins within the first month following the start of treatment with OCABILE and usually becomes less severe over time..

Very common side effects (may affect more than 1 in 10 people):

• Stomach pain

• Feeling tired

Common side effects (may affect up to 1 in 10 people):

• Thyroid hormone irregularity

• Dizziness

• Fast or irregular heart beat (palpitations)

• Pain in the mouth and throat

• Constipation

• Dry skin, redness of the skin (eczema)

• Rash

• Pain in your joints

• swelling in the hands and feet

• Fever

9.5 How to store OCABILE

STORE PROTECTED FROM LIGHT & MOISTURE, AT A TEMPERATURE NOT EXCEEDING30°C

Keep all medicines out of reach of children.

9.6 Contents of the pack and other information

OCABILE 5

Each film coated tablet contains:

Obeticholic acid 5 mg

The excipients used are Microcrystalline cellulose, Sodium starch glycolate, Magnesium stearate, Hydroxy propyl methyl cellulose, Talcum powder, Polyethylene glycol, Titanium dioxide, Ferric oxide Yellow

OCABILE 10

Each film coated tablet contains:

Obeticholic acid 10 mg

The excipients used are microcrystalline cellulose, Sodium starch glycolate, Magnesium stearate, hydroxy propyl methyl cellulose, Talcum powder, Polyethylene glycol, Titanium dioxide, Ferric oxide red .

10. Details of manufacturer

Akums Drugs & Pharmaceuticals Ltd

At: Plot No. 26A, 27-30, Sector-8A, I.I.E., SIDCUL, Ranipur, Haridwar-249 403, Uttarakhand.

11. Details of permission or licence number with date

4/UA/LL/2014 issued on 23.04.2020

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/OCABILE – 5 and 10 mg /APR -20/01 /PI